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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/779,543	WILLIAMS ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9-13,21,30-32,34 and 35* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,11-13,21,30-32,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on November 29, 2007 is acknowledged. Claims 7, 9-13, 21, and 30-35 are currently pending. In the response, Applicant amended claims 7, 21, and 30, cancelled claims 8 and 33, and added claims 34 and 35. Claim 10 is withdrawn from consideration as being drawn to a non-elected invention. This Office Action contains new grounds of rejection not necessitated by Applicant's amendments to the claims (see sections 6 and 7), and therefore, is made non-final.

Requirement for Information

2. Applicant's response to the previously made requirement for information indicating that SEQ ID NO: 23702 corresponds to a 101 bp exon for BCAP31 on chromosome X and that a probe comprising this nucleic acid sequence is not known to Applicants to be present on a commercially available Affymetrix array is noted (see page 13 of the Remarks filed on November 29, 2007).

Election/Restrictions

3. This application contains claim 10 drawn to an invention nonelected with traverse in the reply filed on February 2, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos: 10/076,555, 09/217,471, 60/068,755, 60/080,664, 60/105,234, 09/297,648, 60/072,910, 60/075,954, 60/080,114, 60/080,515, 60/105,877, 60/080,666, 09/313,292, 60/085,426, 60/085,537, 60/085,696, 09/854,124, 09/400,947, 60/101,900, 09/404,706, 60/102,180, 60/102,161, 60/102,380, 60/103,815, 60/105,877, 10/629,771, 09/611,527, 60/142, 311, 60/142,310, 09/803,719, 60/188,609, 10/609,021, 09/819,150, 60/192,853, 10/615,618, 09/932,076, 60/226,326, 10/012,697, 60/254,648, and 60/275,688, fails to provide adequate support or enablement in the

manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The sequence disclosures of prior-filed Application Nos: 10/076,555, 09/297,648, 09/313,292, 09/854,124, 09/404,706, 10/629,771, 09/803,719, 10/609,021, 10/615,618, 10/012,697, and 60/532,830 are described in Table 161 on pages 63-64 of the instant application's specification. According to this table, only Provisional Application 60/532,830 discloses the instant SEQ ID NO: 23702, and as a result, none of the other prior-filed applications provide adequate support for the method of the instant claims. Thus, the effective filing date of the instant application is the filing date of Provisional Application 60/532,830 (**December 23, 2003**). This filing date has been used for prior art purposes.

Information Disclosure Statement

5. Applicant's submission of an Information Disclosure Statement on August 17, 2007 is acknowledged. A signed copy is enclosed.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 11-13, 21, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 7, 9, and 11-13 are drawn to a method for detecting a cancerous breast, colon, or prostate cell in a test sample from a human subject that comprises detecting an increased amount of a nucleic acid comprising SEQ ID NO: 23702, a full complement of SEQ ID NO: 23702, or a nucleic acid encoded by SEQ ID NO: 23702 in a sample obtained from the subject relative to a control sample.

Claim 21 is drawn to a method for assessing the tumor burden of a subject by measuring the level of a gene product in a test sample obtained from the subject. The gene product comprises SEQ ID NO: 23702, complements of SEQ ID NO: 23702, a nucleic acid encoded by SEQ ID NO: 23702, or a nucleic acid encoded by complements of SEQ ID NO: 23702.

Claims 30-32 and 34 are drawn to a method for diagnosing breast cancer, prostate cancer, or colon cancer in a human comprising detecting an increased level of a nucleic acid comprising SEQ ID NO: 23702, a full complement of SEQ ID NO: 23702, or a nucleic acid encoded by SEQ ID NO: 23702 in a sample obtained from the subject relative to a control sample.

The term "full complement" in claims 7 and 30 does not indicate that the complementary sequence comprises the complete 542 nucleotide complement of SEQ ID NO: 23702. Rather, a "full complement" includes a nucleic acid sequence of any length that is perfectly complementary to SEQ ID NO: 23702. This includes nucleic acids ranging from two nucleotides in length to hundreds of thousands of nucleotides in length. Also, the "complements" recited in claim 21 do not have any length or level of complementarity associated with them. That is, complements falling within the scope of the method of claim 21

include nucleic acid sequences ranging from two nucleotides to hundreds of thousands of nucleotides in length with anywhere from 1% to 100% complementarity to SEQ ID NO: 23702. Thus, whether "full complements" or "complements" are considered, the claimed methods encompass cancerous cell detection, assessment of tumor burden, and cancer diagnosis based on the detection of a member of an extremely large and diverse genus of nucleic acids.

The specification teaches that SEQ ID NO: 23702 is a cDNA that corresponds to an mRNA that is overexpressed in breast, colon, and prostate cancer tissue when compared with normal tissue (see Table 159 on page 897). The specification does not disclose any nucleotide sequences that are complements or full complements of SEQ ID NO: 23702 that are indicative of cancer as broadly encompassed in the claims.

A search of the prior and current art does not reveal a representative number of sequences that support the written description of the broad genus of nucleotide sequences encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "a complement" or "a full complement" of SEQ ID NO: 23702. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the

genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Since the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to the instant claims. A disclosure that does not adequately describe a product cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of complements or full complements of SEQ ID NO: 23702 per Lilly by structurally describing representative complements or full complements of SEQ ID NO: 23702 that are useful for detecting a cancerous cell, assessing tumor burden, or diagnosing breast, colon, or prostate cancer or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe complements or full complements of SEQ ID NO: 23702 that are useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses SEQ ID NO: 23702, this does not provide a description of the broadly claimed complements or full complements of SEQ ID NO: 23702 that would satisfy the standard set out in Enzo, because the specification provides no structural features coupled to functional characteristics. The specification also fails to describe complements or full complements of SEQ ID NO: 23702 by the test set out in Lilly, because the specification describes only SEQ ID NO: 23702. Therefore, the specification necessarily fails to describe a representative number of such species. As a result, the specification does not provide an adequate written description of complements or full complements of SEQ ID NO: 23702 in order to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method uses, it also fails to adequately describe the method.

Claim Rejections - 35 USC § 112 (Enablement)

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 11-13, 21, 30-32, 34, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of the Invention

The instant claims are drawn to methods of detecting cancerous cells, assessing tumor burden in a subject, and diagnosing cancer in a subject based on the expression level of a specific gene product (SEQ ID NO: 23702). The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The Breadth of the Claims

The instant claims 7, 9, and 11-13 are broadly drawn to methods of detecting a cancerous breast, colon, or prostate cell in any test sample from a human subject based solely on the observation of an increase in the expression level of SEQ ID NO: 23702, a full complement of SEQ ID NO: 23702, or a nucleic acid encoded by SEQ ID NO: 23702. Claim 21 is broadly drawn to a method of assessing the tumor burden resulting from any type of cancer (*e.g.* prostate

cancer, breast cancer, colon cancer, lung cancer, leukemia, melanoma, stomach cancer, cervical cancer, bladder cancer, liver cancer, pancreatic cancer) in a human subject based solely on an observed increase in the expression level of SEQ ID NO: 23702, a complement of SEQ ID NO: 23702, or a nucleic acid encoded by SEQ ID NO: 23702 or a complement thereof. Claims 30-32, 34, and 35 are broadly drawn to methods of diagnosing breast cancer, prostate cancer, or colon cancer in a human subject based solely on an increase in the expression level of SEQ ID NO: 23702 or a full complement thereof.

As noted above, the term "full complement" in claims 7 and 30 does not indicate that the complementary sequence comprises the complete 542 nucleotide complement of SEQ ID NO: 23702. Rather, a "full complement" includes a nucleic acid sequence of any length that is perfectly complementary to SEQ ID NO: 23702. This includes nucleic acids ranging from two nucleotides in length to hundreds of thousands of nucleotides in length. Also, the "complements" recited in claim 21 do not have any length or level of complementarity associated with them. That is, complements falling within the scope of the method of claim 21 include nucleic acid sequences ranging from two nucleotides to hundreds of thousands of nucleotides in length with anywhere from 1% to 100% complementarity to SEQ ID NO: 23702. Thus, whether "full complements" or "complements" are considered, the claimed methods encompass cancerous cell detection, assessment of tumor burden, and cancer diagnosis based on the detection of a member of an extremely large and diverse genus of nucleic acids.

Guidance in the Specification and Working Examples

The specification teaches that observation of an increase in the expression level SEQ ID NO: 23702 is sufficient for detecting any cancerous cell in any organism, assessing the tumor burden resulting from any cancer in any organism, and diagnosing any type of cancer in any organism (see pages 3-5), but only provides specific information regarding the relationship between SEQ ID NO: 23702 and cancer in Working Example 105 (see pages 885-898). In this example, normal and cancerous tissues were collected from human subjects whose cancer status was already known, and RNA was isolated. cDNA probes were then prepared from this RNA and hybridized to arrays of probes (see pages 885-886). The resulting data are presented in Tables 159 and 160 (see pages 894-907).

Table 159 contains the results relevant to the claimed SEQ ID NO: 23702 (see page 897, columns 1-8 of the table). When cDNA from breast cancer patients was hybridized to the array, 17.39-26.09% of the patients showed an increased level of expression of SEQ ID NO: 23702. The number of breast cancer patients studied ranged from 18-23 individuals. In colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). In prostate cancer patients, 0.98 – 3.09% of the patients studied showed an increase in the expression level of SEQ ID NO: 23702. Here, the number of patients studied ranged from 64 individuals (1.56% showed increased expression) to 102 individuals (0.98 – 1.96% showed increased expression).

The specification does not teach in the working examples or elsewhere that the expression level of SEQ ID NO: 23702 is increased in any other types of cancerous cells, such as

liver cancer, skin cancer, or lung cancer cells. The specification also does not teach detection of cancerous cells based solely on the expression of SEQ ID NO: 23702. In the above example, the disease status of the patients who contributed tissue to the study was already known (see page 885). Similarly, the specification does not teach diagnosing any type of cancer or assessing the tumor burden related to the presence of any cancer in any organism based solely on the expression level of SEQ ID NO: 23702. As discussed above, the working example only teaches measuring the expression level of SEQ ID NO: 23702 in human subjects with known disease status and does not correlate the results with tumor burden or reliably diagnose patients with unknown disease status. Finally, neither the specification nor the working examples teach detection of cancerous cells, assessment of tumor burden, or cancer diagnosis based on the detection of a complement or full complement of SEQ ID NO: 23702.

State of the Prior Art and Unpredictability

The art does not teach detecting cancerous cells, assessing tumor burden, or diagnosing cancer based on an observed increase in the expression level of SEQ ID NO: 23702. Regarding these methods, in general, however, the art teaches that it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells, assess tumor burden, and diagnose cancer. For example, Russo et al. (Oncogene (2003) 22: 6497-6507; cited previously) teaches that microarray-based gene expression studies are useful for rapidly assessing differential expression between cancerous and normal cells (see abstract and page 6497, column 2 – page 6498, column 1). However, Russo also teaches that different cancers showed differential expression of different genes (see pages 6498 – 6501, where Russo reviews

the results of microarray-based expression profiling studies in prostate, oral, breast, and ovarian cancers), thereby demonstrating that the expression level of a single gene is unlikely to function in a diagnostic capacity for any type of cancer. Furthermore, Russo teaches that gene expression results can be unpredictable stating, "False microarray data can be generated from degraded mRNA (page 6503, column 2)." Russo also stated that unpredictability often results from the fact that most human tissue samples used for expression analysis are a mixture of different cells (see page 6503, column 2).

The teachings of Srinivas et al. (The Lancet (2001) 2: 698-704; cited previously) further support the conclusion that the claimed methods are highly unpredictable. Srinivas reviewed methods of cancer diagnosis and prognosis based on microsatellite instability, hypermethylation, single nucleotide polymorphisms, gene expression profiling, and proteomics (see abstract). Regarding the use of biomarkers such as differentially expressed genes for diagnostic purposes, Srinivas states, "The initial phase of biomarker discovery used to focus on single-marker-based approaches but, given the complexity of the carcinogenesis process, it would be difficult to correlate sufficiently any single biomarker to a specific cancer (page 699, column 1)."

The teachings of Reinholz et al. (Clinical Cancer Research (2005) 11(10): 3722-3732; cited previously) provide further evidence of the level of unpredictability inherent in the claimed methods. Reinholz measured the ability of five markers, alone and in several different combinations, to accurately detect a specific type of cancer (breast cancer) in human subjects using RT-PCR to detect differential gene expression (see abstract). The resulting data show significant differences in specificity and sensitivity between the five markers (see Table 4 on page 3729), thus illustrating the unpredictable nature of reliably and reproducibly detecting even

a single type of cancer in a human subject based on the observed expression level of a single gene. Reinholz specifically commented on the limitations of using a single marker for cancer detection stating, "Although *mammaglobin* is a promising tumor marker, it is not universally expressed in all breast cancers. Our results showed that ~20% of invasive breast cancer patients did not have detectable levels of *mammaglobin*. Therefore, we evaluated the utility of adding *B305D-C, B726P, GABA* A_{π}, or *CK-19* to the analysis of *mammaglobin* to discriminate between patients with benign and invasive breast cancer breast biopsies. Our results showed that combining *mammaglobin* with *B305D-C* improved both sensitivity and specificity (page 3730, column 2)."

Furthermore, the disclosure of the instant application supports the conclusion that the claimed methods are highly unpredictable. As discussed above, Table 159 demonstrates that number of patients showing a statistically significant increase in expression of SEQ ID NO: 23702 varied widely between and within the cancer types tested. For example, in colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). Also, although the number of breast cancer patients showing increased expression levels of SEQ ID NO: 23702 did not show this extent of intra-cancer variation, the results differed markedly when compared to the colon and prostate cancer patients. These results clearly demonstrate the level of unpredictability present in the claimed methods.

Finally, the variability in the claimed methods observed with SEQ ID NO: 23702 would necessarily extend to complements or full complements of SEQ ID NO: 23702. As discussed in section 6, the genus of nucleic acids comprising complements or full complements of SEQ ID

NO: 23702 is very large and includes hundreds of millions of structurally and functionally distinct nucleic acids. It is inherent that the ability of these different nucleic acids with lengths ranging from two nucleotides to hundreds of thousands of nucleotides and levels of complementarity with SEQ ID NO: 23702 ranging from 1% to 100% will possess different levels of utility as diagnostic markers of breast cancer, colon cancer, and prostate cancer. Thus, it is clear that the claimed methods are highly unpredictable.

Quantity of Experimentation

The quantity of experimentation required in this case is immense, because it would require significant study and experimentation including trials with hundreds of patients to determine that increased expression of the claimed polynucleotide is capable of reliably functioning to detect even one type of cancer in human subjects. Additional experimentation would be required to demonstrate that over-expression of the claimed polynucleotide reliably functions as a reliable indicator of tumor burden related to the presence of a specific cancer in human subjects. Even further experimentation would be required to demonstrate that an increase in the expression level of the claimed polynucleotide is an accurate and reliable diagnostic agent, capable of diagnosing even a single type of cancer in human subjects. The amount of experimentation required in any of the above cases would be an inventive, unpredictable and difficult undertaking in itself, requiring years of inventive effort, with no guarantee of success at the conclusion. Furthermore, each different complement or full complement of SEQ ID NO: 23702 would require the same extensive trial-and-error type experimentation in order to determine its ability to be used to practice the claimed methods.

The teachings in the pre- and post-filing art support this conclusion regarding the quantity of experimentation required to practice the claimed methods. For example, Feng et al. (Critical Reviews in Clinical Laboratory Sciences (2006) 43(5-6): 497-560; cited previously) teaches that although discovery of promising biomarkers occurs with much less experimental effort than previously, validation of clinical utility remains slow and difficult (page 537, last paragraph). Feng stated, "Biomarker discovery may require only a few weeks and a small number of patient samples, whereas its validation may require thousands of samples from multi-center trials (page 537, last paragraph)." In addition, Feng teaches that detection of a differentially expressed gene does not always correlate with an increased level of protein product (page 538, paragraph), thereby illustrating that upon further experimentation, an initially promising biomarker may be eliminated as a useful diagnostic agent upon further testing. The teachings of Mitas et al. (International Journal of Cancer (2001) 93: 162-171; cited previously) also illustrate the fact that validation of differentially expressed nucleic acids as useful diagnostic markers for even one type of cancer in human subjects requires extensive experimentation with no guarantee of success. Mitas analyzed the expression level of 12 cancer-associated genes by RT-PCR in tissue samples obtained from breast cancer patients (see abstract). Mitas reported that only half of the tested genes accurately functioned as breast cancer indicators in a specific type of breast cancer – metastatic cancer (see abstract and page 166). As added evidence of the quantity of experimentation required for validating a single gene's predictive capabilities in even one cancer type, Mitas further taught that one of the tested genes, VEGF, although not of diagnostic utility for metastatic breast cancer, could be useful in detecting primary breast cancer (page 169, column 1). Thus, Mitas teaches the same marker may not function as an accurate diagnostic

agent for all cancers and further that initially promising genes may not prove to be useful markers upon further analysis. Finally, Srinivas summarizes the extensive effort required to establish the diagnostic value of even a single biomarker in a single cancer in human subject. Srinivas states at pages 702-703:

> The sensitivity, specificity, and predictive value of biomarkers have to be determined through use of body fluids, paired tumours, and surrounding tissue from a wide variety of cancers before they can be used in populations. Many samples from individuals with known characteristics should be processed, to minimize the problems of confounding and to avoid spurious associations. Before field-testing, it should be established that the biomarker is truly in the path of pathogenesis and not merely the result of an adaptive response. Case-control studies on stored samples should be used to test the efficiency of the biomarkers. Although the emerging technologies show great promise, care must be taken to define and establish references or baseline profiles from normal tissue, cells, or body fluids. Extensive animal studies may help refine human testing before screening. The biomarker assay should be reproducible to avoid false-positive and false-negative results and also to provide a substantial lead-time before clinical diagnosis.

Based on these teachings of Feng, Mitas, and Srinivas, it must be concluded that the quantity of experimentation required is very large.

The Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the instant claims are broadly drawn to methods of detecting a cancerous breast, colon, or prostate cell in a human subject, assessing the tumor burden resulting from any cancer in a human, and diagnosing breast cancer, colon cancer, or prostate cancer in a human subject based solely on an observed increase in the expression level of SEQ ID NO: 23702, a complement of SEQ ID NO: 23702, or a full complement of SEQ ID

NO: 23702. Despite the breadth of the claims, the specification only teaches detection of cancerous breast, colon, and prostate cells from human subjects known to have one of these types of cancer, and even these limited results show a high degree of variability (*i.e.* unpredictability). The specification does not disclose the ability of any complement or full complement of SEQ ID NO: 23702 to be used in the claimed diagnostic methods. Furthermore, the specification provides no guidance regarding methods of validation or how to overcome the art-recognized problems of reliable diagnosis based on the expression level of a single gene. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "said sample" in line 1. There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for "said test sample".

Response to Arguments

9. Applicant's arguments, see page 12, filed November 29, 2007, with respect to the objection to the specification have been fully considered and are persuasive. Applicant's amendment to the specification overcomes the objection, and therefore, it has been withdrawn.

Applicant's arguments filed on November 29, 2007 regarding the rejection of claims 7-9, 11-13, 21, and 30-33 under 35 U.S.C. 112, first paragraph as lacking enablement have been fully considered, but they were not found persuasive. This rejection currently applies to claims 7, 9, 11-13, 21, 30-32, 34, and 35.

Applicant first argues that the amendments to the claims overcome the enablement rejection (page 13, last paragraph – page 14, first paragraph). This argument was not found persuasive in view of the new grounds of rejection made with respect to complements of SEQ ID NO: 23702 and full complements of SEQ ID NO: 23702. This argument was also not found persuasive with respect to claim 21, because as discussed above, it is highly unpredictable as to whether the results observed with SEQ ID NO: 23702 can be extrapolated to assess the tumor burden in a human subject with any type of cancer. The references cited previously teach that different genes are often differentially expressed in different cancers, and therefore, the ability to extrapolate an observation of differential expression of a particular gene in one tumor type to another tumor type or to assess tumor burden stemming from any cancer based on the expression level of said gene is highly unpredictable and would require the ordinary artisan to perform undue experimentation.

Applicant also argues that the cited references (Russo, Reinholz) do not suggest that cancer cannot be diagnosed based on differential expression of a single gene (pages 14-15). This

argument was not found persuasive, because the references were cited to highlight the fact that different genes are often differentially expressed in different cancers and that even within patients having the same cancer diagnosis (*e.g.* breast cancer), different genes show differential expression. In other words, the Russo and Reinholz references were cited to indicate that the ability of the expression level of a given gene to serve as a reliable diagnostic marker is highly unpredictable and requires extensive validation and testing.

Applicant also argues that Working Example 105 (discussed above) enables the claimed methods (pages 16-18). This argument was also not found persuasive, because the data presented in this example highlight the unpredictability and variability of the claimed methods. As discussed above, using samples obtained from patients known to have breast cancer, colon cancer, or prostate cancer, SEQ ID NO: 23702 was found to be overexpressed in a variable and non-reproducible manner. For example, the prostate cancer results indicate that SEQ ID NO: 23702 was overexpressed in 3/97 samples, 1/102 samples, 2/102 samples, and 1/64 samples (see Table 159 on page 897). So, samples obtained from patients known to have prostate cancer were accurately diagnosed only 1-3% of the time. This is not a reliable or reproducible diagnostic method. Similarly, breast cancer patients were only accurately diagnosed 17-26% of the time while colon cancer patients were accurately diagnosed anywhere from 12-63% of the time. These results indicate that SEQ ID NO: 23702 is simply unable to reliably and reproducibly diagnose cancer or identify cancerous cells in human subjects. Extrapolation of these results to the assessment of tumor burden resulting from the presence of breast cancer, colon cancer, prostate cancer, or any other cancer encompassed by the method of claim 21 would likewise be a highly unpredictable undertaking requiring undue experimentation.

Finally, Applicant argues that the experimentation required to perform the claimed methods is not undue (pages 16-17). Regarding the issue of undue experimentation, section 2164.06 of the MPEP provides the following guidance, "The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention. '[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance.' In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)." In this case, as discussed above, the specification provides essentially no guidance related to extrapolation of the observed results to other types of cancer or assessment of tumor burden. The specification also fails to provide guidance as to the ability of any other members of the extremely large claimed genus to function in the claimed methods. This lack of guidance in the specification in combination with the inherent unpredictability in the claimed methods requires the ordinary artisan to perform a large quantity of experimentation with little or no starting point and with no guarantee of success. This constitutes undue experimentation.

Since Applicant's arguments were not found persuasive, the rejection of claims 7, 9, 11-13, 21, 30-32, 34, and 35 under 35 U.S.C. 112, first paragraph as lacking enablement has been maintained.

Conclusion

No claims are currently allowable. The claimed methods are free of the art, but they have been rejected for other reasons, specifically failure to comply with the written description and enablement requirements of 35 U.S.C. 112, first paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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AMB

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